

Attorney Docket No. 21208
Serial No. 09/495,556

2

D1

particles in suspension. The floating particles are then sprayed with an aqueous suspension to provide a coating, while drying at the same time. Inlet temperature, spray rate, and air throughput must be adjusted to provide optimum end product. Furthermore, the finished particles must be subjected to a post-drying period at around 40°C, where any residual moisture can be driven off. In some case, this last drying period may be up to 24 hours.

In the specification, please replace the paragraph starting on page 3, line 15, with the following:

Many of the polymers that are used to provide sustained-release properties to powders in the fluid bed process require solvents such as acetone, isopropyl alcohol, chlorinated solvents, alkanes, methyl ethyl ketone, cyclohexane, toluene, carbon tetrachloride, chloroform, and the like. Evaporation of the solvents becomes an environmental concern, and in many states it is illegal to release these emissions into the atmosphere. Aqueous or water based polymers are limited mainly to ethyl cellulose and methacrylic acid esters such as poly methacrylate dispersions. In addition, 10-20% of a suitable plasticizer such as triethyl citrate must be added to the polymer. For example, U.S. Patent No. 5603957 uses a solvent-based polymer system to deliver aspirin over a 24-hour period. Preferred solvents are acetone/alkanol mixtures, or cyclohexane, toluene, or carbon tetrachloride. Castor oil, a low melting point oil, is also included in the polymer solvent mix.

D2

In the specification, please replace the paragraph starting on page 6, line 19, with the following:

D3

In accordance with the invention, there is provided a microsphere that is produced by mixing the therapeutic agent with a hot vegetable oil with a melting point at least above 110°C, and preferably about 160 degrees F, in a vertical or horizontal high intensity shear mixer until the particles or the core substance are thoroughly mixed with the oil, and then cooling the hot melt to produce fine particles that exhibit excellent sustained-release properties. Surprisingly, the entire process can be completed in about 10 minutes or less, utilizing the work input of the mixer to melt the oil and intimately mix it with the core agent. The ideal high temperature melting point oil for this process is

Attorney Docket No. 21208
Serial No. 09/495,556

3

D3 a hydrogenated soy oil with a maximum iodine value of 5.0 and a melting point of 150-160°C. Such an oil with these specifications is Dritex S® in flake form or Sterotex HM® which is a spray chilled, powder. Both are available from AC Humko, Memphis TN. The melting point profile is more uniform if the spray chilled powder is used.

In the specification, please replace the paragraph starting on page 7, line 30, with the following:

D4 Oils such as low melting point vegetable oil, castor oil, baby oil, margarine, cocoa butter, paraffin, and the like have also been used in the pharmaceutical industry for a variety of purposes, but not as sustained-release agents. For example, soft oils are often used for suppositories. These oils cannot be used to provide solid particles at room temperature. Various resins and shellac have also been used, but usually not for sustained-release. Carnauba wax is widely used in pharmaceutical dosage forms.

In the specification, please replace the paragraph starting on page 8, line 27, with the following:

D5 The core material may be selected from any suitable drug, therapeutic or prophylactic agent, nutritional agent, biological substance, fungicide, food or botanical substance, fertilizer, or animal feed, which can be incorporated in the hot melt without losing substantial activity for the chosen therapy. A broad range of materials is therefore useful. Representative non-limiting classes of drugs or nutritional agents useful include those falling into the following therapeutic categories:

In the specification, please replace the paragraph starting on page 9, line 22, with the following:

D6 Non-limiting examples of specific therapeutic agents which may be useful in the present invention can be chosen from the list which follows. Mixtures of these agents and their salts used for appropriate therapies are also contemplated: acetaminophen; acetic acid, acetylsalicylic acid and its buffered form; albuterol and its sulfate; alcohol; alkaline phosphatase; allantoin; aloe; aluminum acetate, carbonate, chlorhydrate, hydroxide-alprozolam; amino acids; aminobenzoic acid; amoxicillin; ampicillin; ansacrine; amsalog; anethole; ascorbic acid; aspartame; aspirin; atenolol;

Attorney Docket No. 21208
Serial No. 09/495,556

4

bacitracin; balsam peru; BCNU (carmustine) beclomethasone dipropionate; benzocaine; benzoic acid; benzophenones; benzoyl peroxide; betahanechol; biotin; bisacodyl; bornyl acetate; brompheniramine maleate; buspirone; caffeine; calamine; calcium; calcium carbonate; casinate and hydroxide; camphor; captopril; cascara sagrada; castor oil; cefaclor; cefadroxil; cephalexin; cetylalcohol; cetylpyridinium chloride; chelated minerals; chloramphenicol; chlorcyclizine hydrochloride; chlorhexidine gluconate; chloroxylenol; chloropentostatin; chlorpheniramine maleate; cholestyramine resin; choline bitartrate; chondrogenic stimulating protein; cirnetidine hydrochloride; cinnamedrine hydrochloride; citalopram; citric acid; cocoa butter; cod liver oil; codeine and codeine phosphate; clonidine and its hydrochloride salt; clorfibrate; cortisone acetate; ciprofloxacin HCl; cyanocobalamin; cyclizine hydrochloride; danthron; dexbrompheniramine maleate; dextromethorphan hydrobromide; diazaparn; dibucaine; diclofenac sodium; digoxin; diltiazem; dimethicone; dioxybenzone; diphenhydramine citrate; diphenhydramine hydrochloride; docusate calcium, potassium and sodium; doxycycline hyalate; doxylamine succinate; esfaroxan; enalpril; enoxacin; erythromycin; estropipate; ethinyl estradiol; ephedrine; epinephrine bitartrate; erythropoietin; eucalyptol; ferrous fumarate, gluconate and sulfate; folic acid; fosphenytoin; 5-fluorouracil (5-FU) fluoxetine HCl; furosemide; gabapentin; gentamicin-gemfibrozil; glipizide; glycerin; glyceryl stearate; griseofulvin; growth hormone; guaifenesin; hexylresorcinol; hydrochlorothiazide; hydrocodone bitartrate; hydrocortisone and its acetate; 8-hydroxyquinoline sulfate; ibuprofen; indomethacin; inositol; insulin; iodine; ipecac-, iron; isoxicam; ketamine; kaolin; lactic acid; lanolin; lecithin; leuprolide acetate; lidocaine and its hydrochloride salt; lisinopril; liotrix; lovastatin; luteinizing hormone; LHRH (luteinizing hormone releasing hormone); magnesium carbonate, hydroxide, salicylate; trisilicate; mefenamic acid; meclofenamic acid; meclofenamate sodium; medroxyprogesterone acetate; methenamine mandelate; menthol; meperidine hydrochloride; metaproterenol sulfate; methyl nicotinate; methyl salicylate; methylcellulose; methsuximide; metronidazole and its hydrochloride; metoprolol tartrate; miconazole nitrate; mineral oil; minoxidil; morphine;

Attorney Docket No. 21208
Serial No. 09/495,556

5

naproxen and its sodium salt; nifedipine; neomycin sulfate; niacin; niacinamide; nicotine; nicotinamide; nitroglycerin; nonoxynol-9; norethindone and its acetate; nystatin; octoxynol; octoxynol 9; octyl dimethyl PABA, octyl methoxycinnamate; omega-3 polyunsaturated fatty acids; ormeprazole; oxolinic acid; oxybenzone; oxtriphylline; para-aminobenzoic acid (PABA); padimate O; paramethadoine; pentastatin; peppermint oil; pentaerythriol tetranitrate; pentobarbital sodium; pheniramine maleate; phenobarbital; phenol; phenolphthalein; phenylephrine hydrochloride; phenylpropanolamine and its hydrochloride salt; phenytoin; phenelzine sulfate; pirmenol; piroxicam; polymycin B sulfate; potassium chloride and nitrate; prazepam; procainamide hydrochloride; procaterol; propoxyphene and its HCl salt; propoxyphene napsylate; pramiracetin; pramoxine and its hydrochloride salt; propranolol HCl; pseudoephedrine hydrochloride and sulfate; pyridoxine; quinapril; quinidine gluconate and sulfate; quinestrol; ralitoline; ranitidine; resorcinol; riboflavin; salicylic acid; sesame oil; shark liver oil; simethicone; sodium bicarbonate; citrate and fluoride; sodium monofluorophosphate; sucralfate; sulfanethoxazole; sulfasalazine; sulfur; tacrine and its HCl salt; theophylline; terfenidine; thioperidone; trimethrexate; triazolam; timolol maleate; tretinoïn; tetracycline hydrochloride; tolmetin; tolnaftate; triclosan; triprolidine hydrochloride; undecylenic acid; vancomycin; verapamil HCl; vidaribine phosphate; vitamins A, B, C, D, B1 B4, B2, B 6, B12, E, K; witch hazel; xylometazoline hydrochloride; zinc; zinc sulfate; zinc undecylenate.

D7
In the specification, please replace the paragraph starting on page 11, line 16, with the following:

The inventive compositions have great versatility in their application. The compositions can be used for wound management such as by direct application to burns, abrasions, skin diseases or infections and the like. Other uses such as packing agents for nasal wounds or other open wounds are also contemplated.

D8
In the specification, please replace the paragraph starting on page 12, line 5, with the following:

Useful additives include, for example, gelatin, vegetable proteins such as sunflower protein, soybean proteins, cotton seed proteins, peanut proteins,

Attorney Docket No. 21208
Serial No. 09/495,556

6

rape seed proteins, blood proteins, egg proteins, acrylated proteins; water-soluble polysaccharides such as alginates, carrageenans, guar gum, agar-agar, gum arabic, and related gums (gum ghatti, gum karaya, gum tragacanth), pectin, water-soluble derivatives of cellulose: alkylcelluloses, hydroxyalkyl celluloses and hydroxyalkylalkylcelluloses, such as methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose, hydroxpropylmethylcellulose, hydroxbutylmethylcellulose, cellulose esters and hydroxyalkylcellulose esters such as: cellulose acetate phthalate (CAP), carboxyalkylcelluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters such as carboxymethyl cellulose and their alkali metal salts; water-soluble synthetic polymers such as polyacrylic acids and polyacrylic acid esters, polymethacrylic acids and polymethacrylic acid esters, polyvinylacetates, polyvinylalcohols, polyvinylacetatephthalates (PVAP), polyvinylpyrrolidone (PVP), PVP/vinyl acetate copolymer, and polycrotonic acids; also suitable are phthalated gelatin, gelatin succinate, crosslinked gelatin, shellac, water-soluble chemical derivatives of starch, cationically modified acrylates and methacrylates possessing, for example, a tertiary or quaternary amino group, such as the diethylaminoethyl group, which may be quaternized if desired; and other similar polymers.

In the specification, please replace the paragraph starting on page 12, line 22, with the following:

Processing aids such as sucrose, polydextrose, dextrose, maltodextrin, lactose, maltose, and the like may also be used. In some cases where accelerated release is desired, a sugar may be incorporated into the hot melt. Since the oil coating is hydrophobic, incorporating a hydrophilic sugar in the hot melt helps counteract the tendency of the particles to float. The sugar also helps to increase the rate of release of the core material by providing solubility to the matrix. Sugar may be present in the melt from 1-30% by weight of the finished particles. In some embodiments of the present invention, the sugar is present in the melt from 5-20% by weight of the finished particles. For example, the sugar may be present in the melt at about 10% by weight of the finished particles. Other substances such as calcium carbonate or other

Attorney Docket No. 21208
Serial No. 09/495,556

7

D9

minerals can be added to provide weight to the particles and affect the release profile.

In the specification, please replace the paragraph starting on page 13, line 6, with the following:

Example 1:

Niacin (nicotinic acid) is added to a plow mixer, which was capable of operating at high temperatures because it was jacketed with a second layer to allow hot water to flow around the vessel. The unit was fitted with a tower-mounted, hydraulic atomizing nozzle with heated tanks and heated/insulated lines to enable hot oil to be applied at high temperatures. A high speed chopper operating at 10 hp was fitted at the discharge point. Hydrogenated soy oil flakes(Dritex S®, AC Humko, Memphis, TN) with a melting point of about 80°C or 140-160°C was sprayed on the powder as it was mixing in vessel. Efficient coating or microencapsulation of the powder was achieved in about 30 minutes when a temperature of about 155°F was reached and the hot oil thoroughly mixed with the powder. Cooling was achieved by discharging the batch into a cooler mounted directly below the mixer. The resulting granules were small, free flowing, and exhibited sustained-release properties when a dissolution test was conducted. The weight percent of the niacin in the finished product was 90%, and the hydrogenated soy oil was 10%.

D10

Please insert the following paragraph on page 8, line 20:

Animal or vegetable oils may be used in the present invention. Such oils may have a melting point between 120 degrees F. and 200 degrees F. In one embodiment, the oils may have a melting point of 110-200 degrees F. In another embodiment, the oils may have a melting point of 120-180 degrees F. For example, hydrogenated soy oil having a melting point of about 160 degrees F. may be used. Hydrogenated soy oil may also have a melting point in the range of about 145-160 degrees F. Another example of an oil for use in the present invention is hydrogenated vegetable oil with a melting point above 110 degrees F.

D11

Please insert the following paragraph on page 8, line 25:

The oils used in the present invention may be provided in an amount such that the finished sustained-release particle contains oil in about 3% to 50% by